DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

To: Administrative File:
STN 125508/0 (DCC Login ID#574313) GARDASIL® 9 (Human Papillomavirus 9-Valent Vaccine, Recombinant)

From: CDR Jeremy L. Wally, PhD, Facilities Reviewer, OCBQ/DMPQ/MRB2

Through: John A. Eltermann, Division Director, OCBQ/DMPQ

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Subject: New Biologics License Application

Indication /Drug Info: Prevention of Human Papillomavirus Types 6, 11, 16, 18, 31, 33, 45, 52, 58

Applicant: Merck Sharp & Dohme Corp.

License Number: 0002

Facility Sites: ----------(b)(4)----------

Action Due Date: December 10, 2014

Recommendation: Approval with the following items to be evaluated during the next Team Biologics inspection:

- Merck has committed to perform a study validating the cleaning of HPV Type 58 from the ----------(b)(4)---------- by early 2015. Completion of this study and acceptability of the results should be confirmed.

- Merck has observed ----------(b)(4)---------- used to formulate the 9-valent HPV vaccine bulk product and determined that these (b)(4) particles originate in the ---(b)(4)---. The CAPA implemented to address these particles appears to have

been successful, since no particles have been observed since August 2012. However, the cause and scope of this issue as well as the impact of these (b)(4) particles on lots of vaccines manufactured in ---(b)(4)--- should be evaluated.

Product Summary

GARDASIL® 9 [henceforth referred to as the 9-valent Human Papillomavirus (HPV) vaccine] is a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and is indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV Types 16, 18, 31, 33, 45, 52, and 58, genital warts (condyloma acuminata) caused by HPV Types 6 and 11, and precancerous or dysplastic lesions (cervical intraepithelial neoplasia [CIN] grade 2/3, cervical adenocarcinoma *in situ* [AIS], CIN grade 1, vulvar intraepithelial neoplasia [VIN] grade 2 and grade 3, vaginal intraepithelial neoplasia [VaIN] grade 2 and grade 3, and anal intraepithelial neoplasia [AIN] grades 1, 2, and 3) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and in boys 9 through 15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts (condyloma acuminata) caused by HPV types 6 and 11, and precancerous or dysplastic lesions (AIN grades 1, 2, and 3) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Each 0.5 mL dose is formulated to contain 30, 40, 60, 40, 20, 20, 20, 20 and 20 μg of HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 L1 proteins, respectively. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate. The final container is a sterile suspension for intramuscular injection in a single-dose vial or a prefilled syringe, to be administered as a 3-dose regimen.

Contents of Submission

This is an electronic submission in eCTD format. The original submission contains regional information including an FDA Form 356h listing relevant facility information, a cover letter and a request for a categorical exclusion, common technical document summaries for quality, nonclinical and clinical information, quality information including relevant information regarding the manufacture and testing of the drug substances and drug product, facility-related appendices and referenced literature, nonclinical study reports for pharmacology and toxicology studies, and clinical study reports and data. Only facilities- and equipment-related information was reviewed including the entirety or portions of Sections 1.1.2 FDA Form 356h, 1.2 Cover Letter, 1.12.4 Request for Categorical Exclusion, 2.3 Quality Summary, 3.2.S Drug Substance, 3.2.P Drug Product, and 3.2.A. Facilities and Equipment Appendix. The reviewed amendments contain FDA Forms 356h, cover letters and, in Section 1.11, partial or complete responses to the information requests of May 30 and August 25, 2014, or telecon of November 6, 2014, and in the June 30 and September 8, 2014 amendments, autoclave sterilization developmental and validation protocols and data in Section 3.2.A.

Environmental Assessment - Categorical Exclusion

Merck has requested a categorical exclusion from the preparation of an environmental assessment for the 9-valent HPV vaccine pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act as provided in §21 CFR 25.31(c) for an action on a Biologics License Application (BLA) if approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. Merck also states that extraordinary circumstances as referred to in §21 CFR 25.21 do not apply.

Reviewer's Comment: *A categorical exclusion has been submitted under 21 CFR § 25.31(c). Merck states that to the their knowledge, no extraordinary circumstances exist and that approval of this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The categorical exclusion claim is therefore acceptable.*

Review

An information request was emailed to Merck on May 30, 2014, and Merck responded in amendments received on June 19 (STN 125508/0/19), June 26 (STN 125508/0/20), June 30 (STN 125508/0/21), July 21 (STN 125508/0/26), and September 8, 2014 (STN 125508/0/33). The information provided in the June 20, 2014 amendment, regarding autoclave sterilization validation (developmental study results and performance qualification protocols), was discussed during a telecon of July 10, 2014, and additional clarification was provided in a follow-up email from Merck of July 11, 2014 and the July 21, 2014 amendment. The results of the new autoclave sterilization validation were provided in the September 8, 2014 amendment. A second information request was emailed to Merck on August 25, 2014, and additional clarification was provided during a telecon of August 27, 2014. Merck responded in an amendment received on September 23, 2014 (STN 125508/0/37). Clarification of the information provided in the amendments of September 8 and 23, 2014, was obtained during a telecon of November 6, 2014, and Merck responded in an amendment received on November 10, 2014 (STN 125508/0/42). This review covers the relevant information submitted in the original submission and the June 19, June 26, June 30, July 21, September 8, September 23 and November 10, 2014, amendments. The scope of this review is based on the impact of the changes reported to the licensed manufacturing process and to the associated facilities and equipment.

Manufacturer

The 9-valent HPV vaccine is a new product formulated using Drug Substance (DS) from the nine HPV Types. Four of the nine HPV Types (6, 11, 16, and 18) are currently approved for the manufacture and formulation of Merck's quadrivalent HPV vaccine (GARDASIL). The original facilities used to perform process validation of DS for commercial manufacture of the quadrivalent HPV vaccine were the ----------(b)(4)----------. Subsequent to the approval of the initial BLA for the quadrivalent HPV vaccine, ----------(b)(4)----------

----------(b)(4)----------.

Bulk manufacturing operations for the 9-valent HPV vaccine are performed at the ----------(b)(4)---------- sites with the following addresses:

- ----------(b)(4)----------
- ----------(b)(4)----------

Routine testing of the ----------(b)(4)---------- is performed at either the ----------(b)(4)----------.

All quality control testing of the 9-valent HPV vaccine is performed at the ---(b)(4)--- site. Secondary packaging of the 9-valent HPV vaccine for both vials and syringes is performed at the ---(b)(4)--- site and at Merck Sharp & Dohme Corp., ----------(b)(4)----------.

The following facilities are used for the manufacture of 9-valent HPV vaccine:

Process Step	Facility	Site	Output
---------(b)(4)----------	(b)(4)	-----(b)(4)-----	----------(b)(4)-----
	(b)(4)	---------(b)(4)---------	----------(b)(4)-----
---------(b)(4)----------	(b)(4)	-----(b)(4)-----	----------(b)(4)-----
	(b)(4)	---------(b)(4)--------	----------(b)(4)----------
---------(b)(4)----------	(b)(4)	------(b)(4)------	----------
	(b)(4)	----------(b)(4)---------	----------(b)(4)---------- ----------
---------(b)(4)----------	(b)(4)	-----(b)(4)-----	----------(b)(4)----------
	(b)(4)	-----(b)(4)-----	(b)(4)
Filling into Vials or Syringes	(b)(4)	-----(b)(4)-----	Clean and sterile equipment used for manufacture of 9-valent HPV vaccine
	(b)(4)	-----(b)(4)-----	9-valent HPV vaccine
Vial or Syringe Inspection	(b)(4)	-----(b)(4)-----	9-valent HPV vaccine
	(b)(4)	-----(b)(4)-----	9-valent HPV vaccine

----------(b)(4)----------
----------(b)(4)----------.

Drug Substance

Description of the Drug Substance

The DS consists of the ----------(b)(4)----------

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----------(b)(4)----------.

Drug Product

Description of the Drug Product

The 9-valent HPV vaccine is a sterile, white cloudy liquid suspension prepared from the HPV Type 6, 11, 16, 18, 31, 33, 45, 52, and 58 -(b)(4)- (a total of 320 µg/mL of L1 protein and --------(b)(4)-- of amorphous aluminum hydroxyphosphate sulfate adjuvant) -------(b)(4)------. Each -(b)(4)- also contains ----------(b)(4)----------. The aluminum content per dose for the 9-valent HPV vaccine (500 µg) is greater than for the quadrivalent HPV vaccine formulation (225 µg) based upon ----------(b)(4)----------. The product is prepared from ----------(b)(4)----------, and is processed and filled using aseptic processing. Sterility testing is included as part of release testing for every lot.

The vaccine is filled into single-dose vials or syringes to ensure a minimum recoverable volume of ----------(b)(4)----------. The particles settle during storage, requiring a mild shaking of the vials or syringes to regain full suspension before use. The ----------(b)(4)----------, and are ----------(b)(4)----------, respectively.

Batch Formula

The formulation batch size of 9-valent HPV vaccine is fixed at a ----------(b)(4)----------:

-----(b)(4)-----

----------(b)(4)----------.

----------(b)(4)----------.

Description of the Drug Product Manufacturing Process

Manufacturing Process Overview

The manufacturing process for the 9-valent HPV vaccine Final Container (FC) in vials or syringes consists of two main steps: formulation and filling. ----------(b)(4)----------. In the detailed description of each of the steps described below, the product contact equipment and room number by building is provided.

Detailed Description of the Manufacturing Process

-------***(b)(4)***----------

-------(b)(4)----------.

----------(b)(4)----------

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-----(b)(4)-----

---------(b)(4)----------
----------(b)(4)----------:

----(b)(4)----

Drug Product Release Testing
Release testing for the vials and syringe included the following tests (and acceptance criteria):

Test	Samples Tested	Acceptance Criteria
Aluminum	----------(b)(4)--------	----------(b)(4)--------
-----(b)(4)-----	----------(b)(4)--------	----------(b)(4)--------
Characteristics	NA	White due to alum suspension, cloudy liquid
----------(b)(4)----------	----------(b)(4)--------	----------(b)(4)--------
General Safety	NA	No weight loss or death

Test	Samples Tested	Acceptance Criteria
Identity	HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58	Presence of the type-specific VLPs confirmed
-----*(b)(4)*------	--(b)(4)--	--(b)(4)--
(b)(4)	(b)(4)	---(b)(4)---
Sterility	NA	No observed microbial growth
Volume of Fill	Vials	Minimum 0.5 mL
	Syringes	--------(b)(4)--------
Syringeability	Syringes	No evidence of needle blockage

*Internal release requirement. The worldwide core regulatory release requirement is a -------(b)(4)--------.

The results of the following in-scope release testing are provided in the submission:

---(b)(4)---

Media Fills

----------(b)(4)----------

----------. The media fills were considered satisfactory after three consecutive challenges showed no turbidity and growth promotion testing of the media was confirmed. The following results are provided in the submission:

---(b)(4)---

Environmental monitoring conducting during the vial and syringe filling media fills had no action level excursions for particulate air, microbial air, or RODAC surface testing.

Reviewer's Comment: *It is not clear if the syringe filling media fills were conducting using the syringes to be used for the 9-valent HPV vaccine. In addition, it is not clear if the vial and syringe filling media fills were conducting using worst-case conditions or any approved interventions, or how the volume of the fills compares to the maximum volume for the 9-valent HPV vaccine. Clarification of these issues was requested from Merck in the Information Request of August 25, 2014 (comment #9). In Merck's response of September 23, 2014, they stated that the media fills were conducted using the syringes to be used for the 9-valent HPV vaccine. In addition, they stated that the media fills conducted to simulate the formulation, syringe filling and vial filling included ----------(b)(4)----------. For both formulation and filling process simulations, incubation times and temperatures were established for the growth promoting media once it was delivered to the laboratory. Regarding the volume used during the media fills, ----------(b)(4)----------. This information*

supports that the media fills were performed using worst-case conditions and using a similar volume as compared to routine production. No further action on these issues is warranted.

----(b)(4)----
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----------(b)(4)----------

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Drug Product Container Closure System

Vials

The 9-valent HPV vaccine may be supplied in a vial containing the following components:

Component	Description	Compendial Compliance
Vial	3 mL, ---------(b)(4)---------- clear tubing glass vial, 13 mm finish	----(b)(4)----
Vial Stopper	13 mm ----------(b)(4)---------- -------- grey elastomer	----(b)(4)----
Cap	13 mm, 1-piece, aluminum seal with brownplastic flip-off cap	N/A*

*The cap serves as secondary packaging component, and does have any product contact.

The vial and vial stopper are the same as what is approved for the quadrivalent HPV vaccine. In addition, the same vial was used for all 9-valent HPV vaccine clinical supplies to date and is being used in all associated stability studies. The same stopper has been used for all 9-valent HPV vaccine clinical supplies to date.

Physical challenge of crimped vials was performed using the ---(b)(4)--- test. For this test, ----------(b)(4)----------. For all of the vials, no ---(b)(4)--- was detected.

Microbial challenge of uncrimped vials was performed using the -----(b)(4)----- test. For this test,----------. There was no (b)(4) of the challenge micro-organism into any of the (b)(4) samples.

Reviewer's Comment: *It is not clear if a positive control was used for the DP vial CCIT and if so how the positive control was generated. This information was requested from Merck in the Information Request of August 25, 2014 (comment #10). See above for the details of Merck's response.*

Syringes

The 9-valent HPV vaccine may be supplied in a syringe containing the following components:

Component	Description	Compendial Compliance
Syringe Barrel (b)(4)	1.5 mL ----------(b)(4)---------- glass syringe, lubricated with --------(b)(4)-------- silicone, with ---(b)(4)--- plastic rigid tip cap	---(b)(4)---
------(b)(4)------	----------(b)(4)----------	---(b)(4)---
Plunger Stopper	1–3 mL ----------(b)(4)----------	----(b)(4)----
Plunger Rod	Brown plunger rod	NA**

----------(b)(4)----------

**No product contact.

The 9-valent HPV vaccine in syringes has not been used in clinical studies to date. Both syringe barrels are made from -------(b)(4)--------- as the vials used for all clinical supplies and are ----------(b)(4)--------. The syringe plunger stopper is ---------(b)(4)--------. The two syringe barrels, including the tip caps, are considered comparable with regard to compatibility with the product, product stability, and container closure integrity. Both syringe barrels and plunger stopper are being used in ongoing stability studies for the 9-valent HPV vaccine.

Physical challenge of the syringes was performed using the ----(b)(4)----- test. For this test, ------ ---------- ---------- ---------- ----------(b)(4)---------- ---------- ---------- ---------- ----------. For all of the syringes, no ---(b)(4)--- was detected.

Microbial challenge of the syringes was performed using the ------(b)(4)------ test. For this test, ---------- ---------- ---------- ----------(b)(4)---------- ---------- ---------- ---------- ----------. No growth was detected in the syringes after the ---------- ----------(b)(4)---------- ----------.

Reviewer's Comments: *It is not clear if these syringes are the same as what is approved for the quadrivalent HPV vaccine and confirmation was requested from Merck in the Information Request of May 30, 2014 (comment #2a). In Merck's response of June 20, 2014, they stated that for the intended 9-valent HPV vaccine syringe (barrel (b)(4) and plunger stopper 1), the product contact components are the same material of construction as for the licensed quadrivalent HPV vaccine, the plunger rod (non-product contact component) has a different color, a different thread design and slight overall dimensional differences, and the specific format of the syringe barrels is different (the format for syringe barrel (b)(4) includes a rigid threaded tip-cap and a round flange, whereas the licensed quadrivalent HPV vaccine currently uses an -(b)(4)- tip-cap and a cut flange).*

Reviewer's Comments: *No information regarding what syringe performance and functionality testing Merck has performed was provided in the original submission and such information was requested from Merck in the Information Request of May 30, 2014 (comment #2b). In Merck's*

response of June 20, 2014, they stated that syringeability testing (confirms that liquid is dispensed from the needle in an even stream without evidence of needle blockage or other conditions which could interfere with discharge of the product) is in progress for the planned syringe launch image (syringe barrel (b)(4) and plunger stopper 1) as part of stability studies and is performed during routine product batch release. Merck stated that syringeability for syringe barrel (b)(4) has been satisfactorily demonstrated through (b)(4), with testing out to (b)(4) planned. Merck further stated that additional functional testing including ----------(b)(4)---------- is in process, and has demonstrated satisfactory results through ---(b)(4)---, with testing out to ---(b)(4)--- planned. A summary of the results of the performance and functionality testing, including any deviations, was requested from Merck in the Information Request of August 25, 2014 (comment #1). Merck responded in the amendment of September 23, 2014, that functional testing of ----------(b)(4)---------- testing is in process using components representative of the intended market image for V503 syringe (same barrel, plunger, and plunger rod) filled with media. Samples are stored at (b)(4) and data has been obtained from ----------(b)(4)----------. For ----------(b)(4)---------- samples each were tested at ----------(b)(4)----------. For ----(b)(4)---- samples were tested at ----------(b)(4)----------. The data provided in the amendment ----------(b)(4)---------- support acceptable functional performance. Merck reported no deviations during this testing. No further action on this issue is warranted.

Reviewer's Comment: *It is not clear if a positive control was used for the DP syringe CCIT and if so how the positive control was generated. This information was requested from Merck in the Information Request of August 25, 2014 (comment #10). See above for the details of Merck's response.*

Facilities and Equipment

Descriptions of the building in which manufacturing activities for the 9-valent HPV take place are provided below. Since the only major facility change implemented for the 9-valent HPV vaccine is the ----------(b)(4)----------, more detailed information on the environmental monitoring (EM) in this building is provided. Only recent routine EM data for the other buildings is discussed below.

Reviewer's Comments: *Based upon the information provided in the original submission, the identity of all of the new pieces of equipment used to manufacture the 9-valent HPV vaccine is not clear. Merck was asked to provide this list in the Information Request of May 30, 2014 (comment #1). Merck responded in the amendment of June 19, 2014, that there is ----------(b)(4)----------*

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